IMIDAZOLIDINEDIONE DERIVATIVES AS ANTIMALARIAL AGENTS, PREPARATION THEREOF, AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is the U.S. National Phase under 35 U.S.C. §371 of International Application No. PCT/US2009/059455, filed Oct. 2, 2009, designating the U.S. and published in English on May 6, 2010 as WO 2010/051129, which claims priority to U.S. Provisional Application No. 61/102,479, filed on Oct. 3, 2008. The content of these applications is incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

Embodiments disclosed herein relate to new imidazolidinedione derivatives, methods of making these compounds, and methods of using the same to prevent, treat, or inhibit malaria in a subject.

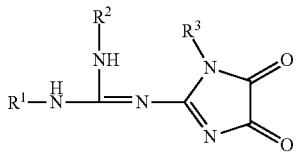
BACKGROUND

There are approximately 350 to 500 million cases of malaria each year. The current global situation with respect to malaria infections is rapidly worsening mainly due to non-availability of effective drugs and development of drug resistance to the existing first line drugs, such as chloroquine and pyrimethamine (C. Plowe, *The Journal of Experimental Biology* 206, 3745-3752 (2003); A. Nzila, *J. Antimicrob. Chemother.* 57, 1043-H154 (2006)). In addition to the drug resistance of the first line antimalarial drugs, the usefulness of many newer antimalarial drugs was impaired by their side effects. Lethal hemolysis side effect was observed in glucose-6-phosphate dehydrogenase (G6PD) deficient recipients of 8-aminoquinoline drugs (primaquine and tafenoquine) (P. Carson et al., *Man. Bulletin of the World Health Organization* 59, 427-437 (1981); E. Beutler, *Blood,* 14 (2), 103-139 (1959)); and CNS toxicity was a problematic side effect in patients treated with mefloquine (P. Phillips-Howard et al., *Drug Safety* 12:370-383 (1995); P. Schlagenhauf, P *J Travel Med* 6:122-123 (1999); H. AIKadi, *Chemotherapy* 53:385-391 (2007)).

SUMMARY OF THE INVENTION

Various embodiments herein relate to a compound having formula I:

(I)



or a tautomer thereof, or their pharmaceutically acceptable salts,

wherein:

R^1 is aryl or heteroaryl, each optionally substituted with one or more R^{1a};

each R^{1a} is independently selected from the group consisting of hydroxyl, carboxyl, halo, aralkyl, amino, alkylamino, dialkylamino, alkoxycarbonyl, alkylsulfonyl, heterocycle, aryl, C_{3-7} cycloalkyl, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy, optionally substituted with up to 5 fluoro;

R^2 is an optionally substituted substituent selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl, C_{3-10} cycloalkyl$(CH_2)_n$—, aryl$(CH_2)_n$—, heteroaryl$(CH_2)_n$—, alkylaryl, heterocyclyl$(CH_2)_n$—, aminoalkyl, $R^{2a}R^{2b}N(CH_2)_n$—, or R^2 is $R^4C(=O)$—, or R^2 is R^5O—;

n is an integer selected from 0, 1, 2, 3, 4, 5, 6, or 7;

R^{2a} is selected from the group consisting of hydrogen, alkoxycarbonyl, alkylsulfonyl, heterocycle, aryl, C_{3-7} cycloalkyl, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

R^{2b} is selected from the group consisting of hydrogen, alkoxycarbonyl, alkylsulfonyl, heterocycle, aryl, C_{3-7} cycloalkyl, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

R^3 is C_{1-10} alkyl optionally substituted with up to 5 fluoro;

R^4 is selected from the group consisting of aryl, heteroaryl, C_{3-7} cycloalkyl, and C_{1-6} alkyl, each optionally substituted with up to 5 fluoro; and

R^5 is an optionally substituted substituent selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl, C_{3-10} cycloalkyl$(CH_2)_n$—, aryl$(CH_2)_n$—, heteroaryl$(CH_2)_n$—, alkylaryl, heterocyclyl$(CH_2)_n$—, aminoalkyl, and $R^{2a}R^{2b}N(CH_2)_n$—.

In some embodiments,

R^1 is aryl optionally substituted with one or more R^{1a};

each R^{1a} is independently selected from the group consisting of halo, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy, optionally substituted with up to 5 fluoro;

R^2 is an optionally substituted substituent selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, aryl, heteroaryl, heterocyclyl$(CH_2)_n$—, aminoalkyl, C_{1-10} alkylC(=O)—, $R^{2a}R^{2b}N(CH_2)_n$—, C_{1-6} alkylO—, C_{2-6} alkenylO—, C_{3-10} cycloalkylO—, arylO—, heteroarylO—, heterocyclylO—, C_{1-6} alkylC(=O)O—, and $R^{2a}R^{2b}N(CH_2)_nO$—,

n is an integer selected from 1, 2, 3, 4, 5, or 6;

R^{2a} is selected from the group consisting of hydrogen, aryl, C_{3-7} cycloalkyl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

R^{2b} is selected from the group consisting of alkoxycarbonyl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

R^3 is C_{1-6} alkyl.

In other embodiments,

R^1 is phenyl optionally substituted with one or more R^{1a};

each R^{1a} is independently selected from the group consisting of halo, C_{1-3} alkyl optionally substituted with up to 5 fluoro, and C_{1-3} alkoxy, optionally substituted with up to 5 fluoro;

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, aryl, heteroaryl, heterocyclyl$(CH_2)_n$—, aminoalkyl, C_{1-10} alkylC(=O)—, $R^{2a}R^{2b}N(CH_2)_n$—, C_{1-6} alkylO—, C_{2-6} alkenylO—, C_{3-10} cycloalkylO—, arylO—, heteroarylO—, heterocyclylO—, C_{1-6} alkylC(=O)O—, and $R^{2a}R^{2b}N(CH_2)_nO$—,

n is an integer selected from 1, 2, 3, 4, 5, or 6;